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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,618	12/17/2001	Guido Henning	Le A 35 010	1214

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Jeffrey M. Greenman
Vice President, Patents and Licensing
Bayer Corporation
400 Morgan Lane
West Haven, CT 06516

EXAMINER	
UNGAR, SUSAN NMN	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 03/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,618	HENNING ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *21 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *2 and 6-8* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1 and 3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed December 21, 2005 in response to the Office Action of June 23, 2005 is acknowledged and has been entered. Previously pending claims 9-11 have been cancelled, claim 1 has been amended. Claims 1 and 3-5 are currently being examined.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are being maintained:

Claim Rejections - 35 USC 112

4. Claims 1, 5 remain rejected under 35 USC 112, second paragraph for the reasons previously set forth in the paper mailed June 23, 2005, Section 5, pages 3-4.

Applicant argues that claim 1 has been amended to recite the critical element. The argument has been considered but has not been found persuasive, the critical element that is lacking is a nexus between the molecule markers and tumor cells and amendment of claim 1 does not address this issue. The rejection can be obviated, for example, by amending claim 1 to recite "detecting at least two tumor molecular markers" if support can be found in the specification as originally filed.

New Grounds of Rejection

Claim Rejections - 35 USC 103

5. Claims 1, 3 and 5 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pillai et al (Cancer Epidemiology, Biomarkers and Prevention, 1996, 5:329-335, IDS item), of record in view of US 20020045591, of record and US Patent No. 6,756,207.

It is noted that the specification teaches, at paragraph 0042 of the published application, that the term "accrediting" refers to the summing of a particular color mixture.

The claims are drawn to a method for detecting tumor cells and their precursors in uterine cervical smears by simultaneously detecting at least two polypeptide molecular markers in a cell or tissue sample comprising contacting the cell or tissue sample with color marked reagents that specifically bind said molecular markers, simultaneously detecting signal intensities of color mixtures resulting from markers and combining and accrediting the signal intensities (claim 1), wherein at least one of the markers present in the combination is p53 or bcl-2 polypeptide (claim 3), wherein three markers are detected (claim 5).

Pillai et al teach a method for detecting tumor cells and their precursors in cervical smears, an assay for the presence of multiple markers for cervical cancer and teach immunofluorescence assay for Bcl-2 using tetramethylrhodamine isothyocyanate antihamster antibodies or p53 in cervical smears using anti-mouse FITC conjugated antibodies (p. 330, col 1) as well as assay for HPV-16 E6 expression (p. 330, col 2), wherein the antibody/marker reagents are clearly color marked reagents that specifically bind said molecular markers. The cells were imaged using an epifluorescence microscope coupled to a low level camera and a digital image analysis system (p. 330, col 2), wherein it is clear that the digital image analysis system automatically reads the sample and processes information drawn to that sample. No HPV-16 E6 staining and little bcl-2 staining was observed in normal cells and p53 staining was found predominantly in the nucleus. When present in smears from patients with cervical disease, p53, bcl-2 and E6 staining was found in cytoplasm (para bridging pages 331-332). A review of Table

1 reveals that ten percent of the smears from Cin I patients presented with three markers, p53, bcl-1 and E6. It would be expected that at least a subset of these smears would present with a cell comprising cytoplasmic p53, bcl-2 and E6, which clearly identifies a precursor of a tumor cell. Further, Table 1 discloses that eleven percent of the smears from invasive cancer patients presented with three markers, p53, bcl-1 and E6. It would be expected that at least a subset of these smears would present with a cell comprising cytoplasmic p53, bcl-2 and E6 which clearly identifies a tumor cell in the uterine cervical smear from a cervical cancer patient.

Pallai et al teach as set forth above but do not teach simultaneously detecting signal intensities of color mixtures resulting from markers and combining and accrediting the signal intensities, does not appear to simultaneously assay for p53, Bcl-2 and E6.

US 20020045591 specifically teaches the conventional use of triple immunofluorescence microscopy (see para 0141 of the Detailed Description).

US Patent 6,756,207 specifically teaches that screening of cells treated with dyes and fluorescent reagents is well known in the art (col 2, lines 37-39). Further, the availability and use of fluorescence-based reagents has helped to advance the development of both fixed and live cell high-content screens. Advances in instrumentation to automatically extract multicolor high-content information has recently made it possible to develop an automated tool for the optical analysis of cells (col 4, lines 34-40) to rapidly determine the distribution and environment of fluorescently labeled reporter molecules in cells (abstract). The specification teaches the conventional analysis of multicolor immunofluorescence microscopy wherein the patent specifically teaches that cell scanning methods can be used to perform many different assays on cellular samples by applying a number of

analytical methods simultaneously. Examples of the assays are (1) the measurement of total fluorescent intensity within the cell nucleus for the multiple fluorescent colors, that is combining and accrediting the signal intensities as disclosed by the specification (2) measurement of the average fluorescent intensity within the cell nucleus for the combined colors (clearly drawn to signal intensities of mixed colors), that is combining and accrediting the signal intensities as disclosed in the specification, (3) measurement of the total fluorescent intensity of a ring outside the nucleus that represents fluorescence the cell's cytoplasm (cytoplasmic mask) for mixed colors, (4) measurement of the average fluorescent intensity of the cytoplasmic mask for each of the multiple colors, (5) measurement of the ratio of the average fluorescent intensity of the cytoplasmic mask to average fluorescent intensity within the cell nucleus for the combined colors, (6) measurement of the difference of the average fluorescent intensity of the cytoplasmic mask and the average fluorescent intensity within the cell nucleus for the combined colors (para bridging columns 18-19). The specification specifically teaches that these methods are useful for rapidly determining the distribution of fluorescently labeled reporter molecules in cells (see abstract), wherein the reporter molecules include fluorescently labeled antibodies (see for example, col 29, para bridging columns 1 and 2, col 32, lines 34-45, col 32, lines 34-46).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have combined the methods of Pallai et al with the conventional methods of both US 20020045591 and US Patent No. 6,756,207 in order to simultaneously immunoassay for bcl-2, p53 and E6 in the smear samples of Pallai et al with conventional triple immunofluorescence microscopy and analysis methods because the conventional triple immunofluorescence

microscopy would save time, labor and reagents in the assay process and the conventional, simultaneous analysis methods would further characterize the identification of the three markers and their localization within the cell and aid in differential identification and detection of tumor cells and their precursors compared to normal cells. One would have been motivated to have combined the methods of Pallai et al with those of US 20020045591 and US Patent No. 6,756,207 in order to simultaneously immunoassay for bcl-2, p53 and E6 in the smear samples of Pallai et al with conventional triple immunofluorescence microscopy and analysis methods in order to speed up analysis, reduce overall costs and to deal with the limited sample volumes presented by the use of smear samples.

6. Claims 1 and 4 are rejected under 35 USC 103 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Pillai et al (Cancer Epidemiology, Biomarkers and Prevention, 1996, 5:329-335, IDS item), of record in view of US 20020045591, of record and US Patent No. 6,756,207, *Supra* and further in view of Kihana et al (Cancer, 1994, 73 :148-153), of record.

The claims are drawn to a method for detecting tumor cells and their precursors in uterine cervical smears by simultaneously detecting at least two polypeptide molecular markers in a cell or tissue sample comprising contacting the cell or tissue sample with color marked reagents that specifically bind said molecular markers, simultaneously detecting signal intensities of color mixtures resulting from markers and combining and accrediting the signal intensities (claim 1), wherein the combination is p53 and her2/neu (claim 4).

Pillai et al, US 20020045591 and US Patent No. 6,756,207 teach as set forth above, but do not teach marker combinations which comprise p53 and her2/neu.

Kihana et al teach the immunoassay of formalin-fixed paraffin-embedded tissue sections of cervical adenocarcinoma for c-erbB-2 protein which was detected in 77% (34 of 44 cases) of the tumor tissues assayed (see abstract and p. 149, col 1) but only in 13% (1 of 8) of the non-tumor samples tested. Thus it appears that given the expression of c-erbB-2, it is more likely than not that a sample that presents with c-erb-2 would be positive for cervical.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the assay of the c-erbB-2 of Kihana et al for either bcl-2 or E6 in the method of the combined references because Kihana et al teach that C-erbB-2 is expressed in the vast majority of cervical carcinoma samples tested. One would have been motivated to include the c-erbB-2 of Kihana et al in the multiple marker assay for cervical cancer in order to detect an additional marker that would give additional information that would be useful in determining the therapeutic approach to the treatment of the patient, since herceptin treatment of cancers expressing C-erbB-2 is well known in the art. One would have had a reasonable expectation of successfully identifying C-erbB-2 in the method of the combined references because Kihana teach that 77% of the samples assayed expressed the C-erbB-2 protein and given the expression of the marker in the majority of cervical carcinoma samples, it is reasonable to expect that the marker would also be present in Pap smear cells as well. Finally, one would expect that at least a subset of the cells of samples from advanced carcinoma patients tested would express at least e-erbB-2 and p53, given the overlap of patients expressing both markers wherein Pallai et al teach that 25% of patients with invasive cancer of the cervix present with p53 (p. 332, Table 1) and the teaching of Kihana et al that 77% of the patients with adenocarcinoma present

with C-erbB2. Given the expression overlap, one would have a reasonable expectation of detecting tumor cells by simultaneously detecting p53 and c-erbB2. Although Kihana et al do not teach that precursor uterine cervical cancer smears express c-erbB2 and neither reference specifically teaches that c-erbB2 is expressed in cervical smear cells, the claimed method appears to be the same as the method of the combined references, absent a showing of unobvious differences. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed method is different from that taught by the prior art combined references and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

7. All other objections and rejections set forth in the previous office action are hereby withdrawn.

8. No claims allowed.

9. Applicant's amendment necessitated the new grounds of rejection. Thus, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

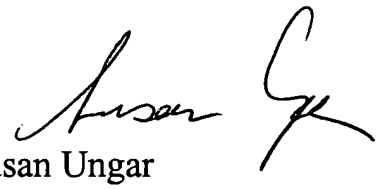
A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT

TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at 571-272-0787. The fax phone number for this Art Unit is (571) 273-8300.

Effective, February 7, 1998, the Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1642.



Susan Ungar
Primary Patent Examiner
March 9 2006